REMARKS

Claims 63-82 are pending in the present application. Entry of the foregoing and favorable reexamination of the subject application, as amended, pursuant to and consistent with 37 C.F.R. § 1.112, and in light of the remarks which follow, are respectfully requested.

Drawings

Figures 1A and 1B, Figure 2, and Figure 3 are objected to. The Office states that these figures are not clear as it is difficult to discern the individual lanes of the presented data. Applicants traverse this objection, noting that the submitted figures represent the best images available to Applicants and that they are typical representations of this type of experimental data. Applicants request withdrawal of this objection.

The Office also states that only Figures 1-10 are presently in the application and Figures 11-16 have therefore not been considered. Applicants submit that Figures 11-16 have been misplaced by the Office. These Figures were submitted at filing, and, in response to Notice to File Missing Parts of Application, formal Figures 1-16 were submitted on September 9, 2002. Applicants have submitted replacement copies of Figures 11-16 for the Examiner's convenience.

Specification

The specification has been objected to as failing to properly indicate trademarks. This objection is moot in view of the present amendments.

The specification has also been objected to because of its arrangement. This objection is also moot in view of the present amendments.

Sequence compliance

The application has also been objected to as failing to comply with the sequence rules. The Office states that sequence identifiers must be provided in the specification and claims. The present amendment adds those sequence identifiers, and this objection may be withdrawn.

Oath/Declaration

The Office has also pointed out that the originally filed declaration of Dr. Roger Brent contains non-initialed alterations. This objection to the Brent declaration is overcome by the filing herewith of a new declaration in this case signed by Dr. Brent. Applicants note that this declaration is submitted pursuant to a request to correct inventorship under 37 CFR 1.48(a). This objection may be withdrawn.

Claim objections

Claims 63 and 79 have been objected to for lack of clarity, claims 64-66, 78, and 80-82 have been objected to for lack of clarity and precision, and claims 67-76 have been objected to as being in improper form because of multiple dependency. These objections are rendered moot by the current claim amendments.

More specifically, claim 63 has been amended to recite "An intracellular recognition molecule," and claim 79 has been amended in order to recite "A dimeric intracellular recognition molecule," as suggested by the Office. Claim 76 has also been amended to recite "An oligomeric intracellular recognition molecule," consistent with the amendments to claims 63 and 79.

Claims 64-65, 78, and 80-82 have been amended to recite "The" at the beginning of the claims, also as suggested by the Office; claim 66 has been

cancelled.

Claims 67-76 have been amended in order to delete the multiple dependencies.

Withdrawal of each of these objections is respectfully requested.

Claim rejections under 35 U.S.C. § 112, first paragraph

Claims 63-66 and 77-82 have been rejected under 35 U.S.C. §112, first paragraph, as being non-enabling for any intracellular recognition molecule or target. This rejection is respectfully traversed in part by claim amendment and in part for the following reasons.

Claim 63 has been amended to recite that the intracellular recognition molecules are peptide aptamers. The Examiner has expressed the opinion, in the office action, that claim 63 was enabled for intracellular molecules that are peptide aptamers. In so far as the rejection pertains to the broad definition of intracellular recognition molecule, this amendment should render it now moot.

Claim 63 has also been amended to recite that the platform is thioredoxin or thioredoxin-like. With regard to these preferred platforms, it is submitted that the specification is enabling. Indeed, the examples of the specification teach the use of *E. coli* thioredoxin as a platform for peptide aptamers. All the necessary information for one skilled in the art to reproduce the invention according to this embodiment is provided, in the specification and in reference 1 (Colas et al, Nature 1996) cited in the description.

With regard to the thioredoxin-like platforms, their definition is given in the specification in paragraph [0059], by reference to *E. coli* thioredoxin. Their manipulation does not require special experimentation for one specialized in molecular biology or genetic engineering. Moreover, one of the inventors, Pierre

Colas, confirms in the declaration enclosed with this reply that use of a thioredoxin-like platform also provides peptide aptamers according to claim 63.1 As stated by Dr. Colas, human thioredoxin, which is an exemplary thioredoxin-like protein, has been used successfully as a platform according to the present invention. Consequently, in so far as the rejection concerns the nature of the platform, it should be traversed by the claim amendment and the inventor's declaration.

Claim 63 has also been amended in order to delete the language "having the capacity to" previously recited. The present amendment makes clear that an intracellular recognition molecule according to claim 63 is a peptide aptamer which interacts with its target molecule T with an affinity corresponding to a K_d value of less than or equal to $5x10^{-9}M$. The rejection, as it pertains to this expression, is rendered moot by this amendment.

Further, claim 63 has been amended to recite that the proteinaceous recognition domain consists of a peptide having a length of five to sixty amino acids. This limitation was previously recited in claim 64. The remark of the Examiner regarding the open and closed language in association with the structure has therefore been addressed.

Moreover, the enclosed Colas declaration confirms that peptide aptamers may be selected against a target protein from libraries of peptide aptamers bearing a variable region of 8, 13, 20 or more amino acids. It is thus submitted that the data provided confirms that peptide aptamers according to the invention may be selected with a variable region in the specified range of 5 to 60, in accordance with the teaching of the present application.

For a given target molecule, i.e., for a predetermined target molecule defined by the skilled artisan, the present specification therefore enables the skilled person

1 An unsigned version of this Colas Declaration is submitted herewith. An identical signed copy will be

to make and use the invention, i.e. to make a peptide aptamer according to claim 63 which binds the predetermined target molecule with an affinity corresponding to a K_d value of less than or equal to $5x10^{-9}$ M. It is submitted that the description provides enough guidance to the skilled person to design and make suitable peptide aptamers.

As indicated in Applicants' specification, the present invention lies in large part in the finding that, for any target molecule, an intracellular recognition partner interacting with a K_d value of less than or equal to $5x10^{-9}$ M can be designed, the recognition partner having the specific structure of a peptide aptamer according to claim 63. This recognition molecule may also be found by screening a library of aptamers having the specific structure mentioned in claim 63.

As the sequence of the recognition domain of a peptide aptamer according to claim 63 is dependent on the target molecule, all aptamers covered by claim 63 cannot be explicitly disclosed in the application. However, the application gives sufficient information for the skilled person to obtain a peptide aptamer interacting with any chosen target molecule with a K_d value of less than or equal to $5x10^{-9}$ M. Confirmation of this point is emphasized in the enclosed declaration of Dr. Pierre Colas, one of the inventors of the present invention, who was able, for different and unrelated target proteins like RasGAP, Fur, Grb2, Raf, ERK1, AKT1, and Hsp70, to select aptamers according to claim 63 interacting with each target respectively. Moreover, it was possible to select aptamers binding said target proteins using different libraries of aptamers with a variable region of either 8, 13, or 20 random amino acids.

The specification and the experimental section of the present application also provide examples of such peptide aptamers. The experimental section provides

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submitted in the near future under separate cover.

sufficient details for preparing a library of peptide aptamers having the thioredoxin protein as a platform and a variable region, inserted into the platform, wherein the variable region is 20 amino acids in length.

Moreover, the claims have been amended to make clear that the peptide aptamers necessarily interact with the target molecule with a K_d value of less than or equal to $5x10^{-9}$ M. This characterizing feature is set forth in all present claims, as recognized by the Examiner.

The specification also teaches another method for obtaining a peptide aptamer interacting with a given target molecule with a K_d value of less than or equal to $5x10^{-9}$ M. Specifically, it is taught in the application that such an aptamer may be obtained by mutation of a primary aptamer, selected for example from a library, the primary aptamer binding the target molecule with an affinity higher than the required K_d value of $5x10^{-9}$ M. In the first example of the present application, aptamer "10", which binds the target Cdk2 with a K_d value higher than $5x10^{-9}$ M, gives rise to the aptamer "10M" by mutation of only 2 out of 20 amino acids of the variable region. The aptamer 10M is shown to interact with Cdk2 with a K_d value below the threshold of $5x10^{-9}$ M. In this respect it is noted that the Examiner has stated at page 10 of the office action that the specification provides no working examples of any variant sequence that is encompassed by the claims. It is respectfully submitted that Aptamer "10M" disclosed in the first Example of the specification is a working example of a variant sequence encompassed by the claims.

In addition, for the record, it is noted that on page 8 of the office action, the Examiner considers that a recognition molecule of the invention comprises a recognition domain which has for example the amino acid sequence QVWSLWALGWRWLRRYGWNM. It is however pointed out that such an

aptamer is not in the scope of the present claims. Indeed, the aptamer having the above-described variable region embedded in the thioredoxin platform, interacts with its Cdk2 target with an affinity which is in the range of 10^{-7}M, that is far above the required threshold of $5x10^{-9}$ M. This point is confirmed in example 1 of the application.

It must also be noted that the application teaches how to screen a library for aptamers which interact with the given target with a K_d value of less than or equal to $5x10^{-9}$ M (see page 7, [0023] and page 26, [0109]).

It is submitted that, contrary to the Office's assertion, the skilled artisan would not recognize a high degree of unpredictability, because the application teaches how a recognition peptide aptamer having the claimed characteristics may be found for **any given target** molecule. The only experimentation needed is to construct a peptide aptamer library, or use an existing library, as taught in the specification, and to screen said library according to the teaching of the specification.

The results obtained by Dr. Pierre Colas, one of the inventors, following the teaching and reported in the enclosed declaration, confirm that peptide aptamers according to claim 63 may indeed be obtained with thioredoxin-like platforms, with a wide variety of variable region lengths in the range 5-60 amino acids, and with very different, unrelated target proteins, thus justifying the current scope of the claims.

In view of the preceding, withdrawal of the rejection is thus respectfully requested.

Claim rejections under 35 U.S.C. § 112, second paragraph

Claims 63-66 and 77-82 have been rejected under 35 U.S.C. § 112, second

paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicant regards as the invention. This rejection should be rendered moot by the present claim amendments.

Specifically, claims 63, 79, and their dependent claims have been amended to delete the phrases "having the capacity to" or "capable of."

Claim 64 has been amended to recite only a preferred range, in association with the term "consists of."

Claim 66 has been cancelled.

And claim 78 has been amended to provide antecedent basis for the recognition molecules according to claim 63.

In view of the preceding, withdrawal of the indefiniteness rejections is respectfully requested.

Claim rejections under 35 U.S.C. § 102

Claims 63-66 and 77-79 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Brent et al, WO96/02561. This rejection is respectfully traversed.

Peptide aptamers disclosed in the reference Brent et al., are **not** in the scope of the present claims. Claim 63 requires that a peptide aptamer of the invention interacts with its target with an affinity equal or less than the K_d value of $5x10^{-9}$ M. However, the peptide aptamers disclosed in the cited reference interact with their target with a K_d value which is **higher** than $5x10^{-9}$ M.

Specifically, peptide aptamers having recognition domains of 20, 38, and 41 amino acids are disclosed at pages 34 and 35 and Figure 3B of Brent et al. It can be deduced from the disclosure of Brent et al. at page 35, lines 15 to 18, and at page 34 line 18 that peptides "3" and "13" are, among the different molecules disclosed,

representative of the strongest binders. It can also be seen from Figure 3B of Brent et al. that peptides "3" and "13" have the following sequences :

Peptide "3" : LVCKSYRLDWEAGALFRSLF

Peptide "13" : SVRMRYGIDAFFDLGGLLHG

From the sequence data, it can thus be determined that these two peptide aptamers are the same molecules as those designated "Pep 2" and "Pep 5" in the publication referred to as "Reference 1" in the present application (Colas et al., Nature, vol.380, 11 April 1996: see in particular Fig 2a of Colas et al.). Moreover, the same "Pep2" and "Pep5" aptamers are referred to in Example 1 of the present application, and their binding affinities are explicitly disclosed as being 64 nM and 52 nM, i.e., 6.4 $x10^{-8}$ nM and 5.2 $x10^{-8}$ nM, respectively (see present application, Example 1, Table 1, and also Colas et al, Table 1). Thus, the two molecules which are representative of the strongest binders disclosed in Brent et al. in fact have binding affinities well above the claimed threshold value of $\leq 5 \times 10^{-9}$ M. Brent et al. therefore cannot anticipate the present claims, and this rejection should be withdrawn.

Claims 63-66 and 77-79 have also been rejected under 35 U.S.C. § 102(b) as being anticipated by Colas et al, Nature, vol.380, 11 April 1996. This rejection is respectfully traversed.

Peptide aptamers disclosed in the reference Colas et al., Nature are also **not** in the scope of the present claims. As indicated above, claim 63 requires that a peptide aptamer of the invention interacts with its target with an affinity equal or less than the K_d value of $5x10^{-9}$ M. However, the peptide aptamers disclosed in Colas, Nature, all interact with their target with a K_d value which is **higher** than

$5x10^{-9}$ M. This is confirmed by the Example 1 of the present application. In this example, the K_d of the interaction between Cdk2 and different peptide aptamers is measured. It is clear from this example that aptamers 8, 5, 2, 11, 10, and 3 referred to in Table 1 are the peptides 8, 5, 2, 11, 10, and 3 disclosed in figure 2B of the cited reference (1), which is the cited Colas et al., Nature reference. Table 1 shows that none of the peptide aptamers, except aptamer 10M which is **not** disclosed in Colas et al., Nature interacts with the target Cdk2 with a constant less than $5x10^{-9}$ M. Thus, as none of the aptamers disclosed in Colas et al., Nature satisfy the current claim limitations, the rejection over Colas, Nature should also be withdrawn.

Claims 63-66 and 77-82 have been further rejected under 35 U.S.C. § 102(b) as being anticipated by Colas et al, TIBTECH, vol.16, August 1998. This rejection is respectfully traversed.

This third document makes reference to the results presented in the above-mentioned publication Colas, Nature, vol.380, 11 April 1996. The 14 peptide aptamers mentioned were selected against the target protein Cdk2 and are those described in figure 2B of the Nature publication. As explained in the preceding section, none of these aptamers interacts with Cdk2 with an affinity less or equal to $5x10^{-9}$ M. Therefore, this third reference (like Colas, Nature) fails to disclose the subject matter of the presently claimed invention and cannot be anticipatory.

Moreover, this publication in TIBTECH does not disclose, nor even suggest, oligomers comprising several peptide aptamers. This publication describes the isolation of 14 peptide aptamers, none of which interact with each other, but only with Cdk2, thus rendering them unable to form oligomers of peptide aptamers. This publication also discloses the interaction between two fusion proteins, one bearing the bait and the other the prey (p.355, right column). However, only the prey is a

peptide aptamer and therefore this interaction does not form a dimer of peptide aptamers. For the preceding reasons, this § 102 rejection may also be withdrawn.

Attorney Address Correction

Applicants note that the present Office action was mailed to the incorrect address. Effective immediately, please address all communication in this application to:

Karen L. Elbing, Ph.D.
Clark & Elbing LLP
101 Federal Street
Boston, MA 02110
Customer No. 21559.

Conclusion

Applicants submit that this application is now in condition for allowance, and such action is respectfully requested. Enclosed is a Petition to extend the period for replying to the Office action for three months, to and including May 4, 2005, and a check in payment of the required extension fee.

If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: 4 May 2005

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